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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/318,870	05/26/1999	ANDREW H. SEGAL	3378/80489	2018

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EXAMINER
BELYAVSKYI, MICHAIL A

ART UNIT	PAPER NUMBER
1644	30

DATE MAILED: 04/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/318,870	SEGAL, ANDREW H.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,13,14,17-20 and 22-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,13,14,17-20 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: Notice to Comply with Sequences Requirements.

DETAILED ACTION

1. The **examiner** of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Michail Belyavskyi, Group Art Unit 1644, Technology Center 1600

Applicant's amendment, filed 2/28/03 (Paper No. 28), is acknowledged.

Claims 1-8, 13-14, 17-20 and 22-25 are pending.

2. Applicant's cancellation of Claims 9-12, 15-16 and 21 in conjunction with Applicant's amendment filed 2/28/03 (Paper No. 28) and declaration filed under 37 CFR1.132 by Dr. Andrew Segal on 2/28/03 (Paper No. 29) has obviated the previous rejections of claims 1-8, 13-14, 17-20 and 22-25 under 35 U.S.C. 112, first paragraph and second paragraph in Paper No. 24 mailed on 10/02/02 .

It is noted that New Grounds of Rejection are set forth herein.

3. This application contains sequences disclosure on page 3, line 13 that ~~are~~ is encompassed by the definitions for amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is reminded of the sequence rules which require a submission for all sequences of 10 or more nucleotides or 4 or more amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules.

Applicant is reminded to amend the specification accordingly.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-8, 13, 14, 17-20 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for at least 20 % increasing in a survival period of vaccinated mice compare to control non-vaccinated mice during B16 cells –initiated melanoma tumor formation comprising vaccinated mice with composition comprising cytokine-coated B16 cells, does not reasonably provide enablement for a method of vaccinating a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine-coated cell comprising said antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification only discloses that mice vaccinated with cytokine-coated melanoma B16 cells will have a considerably longer survival period as compare to control mice (see examples 7-9 in particular).

The claims are drawn to a method of vaccinating a mammals. By definition, a vaccine is a composition to induce a specific immunity that **prevent** or protect against a specific disease caused by a specific agent. One of the criteria for a vaccine is the levels of antibody (humoral immune response) before and after immunization and the success of vaccination is judged by the extent of increase in the level of antigen - specific antibody. The second criterion for a vaccine is the ability to stimulate memory T lymphocytes (cell-mediated immune response) (See Immunobiology, Third Edition, Chapter 13 in particular). The specification provides no information on the immunogenicity of *any* vaccine comprising *any* cytokine-coated cell comprising antigen or the ability of such to protect or prevent from antigen-specific disease. Moreover, Applicant acknowledge that tumors were detected in mice vaccinated with composition comprising cytokine-coated B16 cells (see page 101, line 16-20 in particular). The

specification fails to teach that the vaccine comprising *any* cytokine-coated cell comprising antigen are capable of generating an antibody response. The specification also fails to teach that the antibody response to the claimed *any* cytokine-coated cell comprising antigen thereof, provides for a protection against infection. Vaccines by definition trigger an immunoprotective response in the host vaccinated and mere antigenic response is insufficient. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, S.A. et al. (eds) published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". Moreover, Chandrasheker et al., (US Patent 6,248,329) teach that although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessary correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from specific disease, associated with said antigen (see column 1, lines 35-45 in particular). In addition, Spitler , (Cancer Biotherapy, 1995, v.10 pages 1-3 teaches that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company, and you're likely to get the same response" (see page 1, column 1, paragraph 1 in particular). The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. Ezzell (NIH Research, 1995, Vol.7, pages 46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see entire document, particularly the last paragraph). It is well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Furthermore, no one is very optimistic that a single peptide or a virus carrying the gene encoding that peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (Ezzell; page 48, paragraph 6).

The specification fails to teach that claimed *any* cytokine-coated cell comprising antigen does in fact confer protection from infection, as is requisite of a vaccine composition. The art teaches that the selection of protective antigens from the plethora of protein antigens available is unpredictable. The specification fails to teach that the claimed *any* cytokine-coated cell comprising antigen is able to perform as a vaccine (i.e. protection, reduction in morbidity and/or mortality of disease) and the art does not recognize *any* cytokine-coated cell comprising antigen as operative vaccines. The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. (Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001).

Therefore, it is not clear that the skilled artisan could predict the efficacy of a method of vaccinating a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine-coated cell comprising said antigen exemplified in the specification.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of vaccinating a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine-coated cell comprising said antigen in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 17- 20 and 22-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 17-20 and 22-25 are indefinite and ambiguous in being dependent upon canceled claims 9, 10, 15 and 21.

B. Claim 25 is indefinite and ambiguous in recitation " cytokine is extremely bioactive, natively bioactive or suprabioactive" . The characteristics and metes and bounds of "extremely bioactive, natively bioactive or suprabioactive" are ambiguous and indefinite.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 37(c) of this title before the invention thereof by the applicant for patent.

9. Claims 1, 2, 13, 14, 17-19, 22-25 are rejected under 35 U.S.C. 102(e) as being anticipated by Hiserodt et al. (US Patent 6,277,368).

US Patent '368 teaches a method of vaccinating a mammal, including mouse , to selected antigen, comprising administering a vaccines comprising a primary tumor cells and cytokine-secreting cells (see entire document, Abstract in particular). It is noted that "cytokine-coated cells" of the present invention are obtained by mixing cell that already express an antigen, a tumor cell antigen for example, with engineered cytokines that can become membrane-bound (see page 79 lines 9-25 in particular). US Patent '368 teaches that cytokines secreted by said cytokine-secreting cells are exogenous to primary tumor cells (see column 7, lines 25-40 in particular). US Patent '368 teaches that cytokine is a GM-CSF, that is a ligand for GM-CSF receptor (see column 7, lines 31, or column 10, lines 52-65 in particular). US Patent '368 teaches that said cytokines can be membrane-bound capable of potentiating an immunological response against the tumor-associated antigen (column 15, lines 36-45 in particular). Moreover, US Patent '368 teaches that it is preferable that cytokine attached to the cell membrane to keep it in the vicinity of bystander tumor antigen comprised in the vaccine (see column 16, lines 28-35 in particular). US Patent '368 teaches that when particular cytokines have potent immunostimulatory activity but do not occur naturally in a membrane-bound form, it is possible to engineer membrane-bound forms with a high degree of lipophyllicity (see column 16, line 50-65 in particular). US Patent '368 teaches that said vaccine composition can be attenuated (see overlapping columns 23 and 24 in particular).

Claims 22 and 25 are included because the claimed functional limitation would be inherent properties of the referenced method , because it is clear that both the prior art and claimed invention administer the same treatment to achieve the same results using the same extremely bioactive, natively bioactive or suprabioactive cytokines and cytokine-coated cells that would be unable to divide in vitro . Under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process. See MPEP 2112.02. Since the office does not have a laboratory to test the reference cytokines it is applicant's burden to show that the reference cytokines do not have the same functional limitation as recited in the claims. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

The reference teaching anticipates the claimed invention.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 3-8 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hiserodt et al. (US Patent 6,277,368) in view of the Known fact disclosed in the Specification on pages 52-54 and 66 – 68.

The teaching of US Patent '368 has been discussed, supra. US Patent '368 teaches that cytokines can be engineered to become stable associated with the plasma membrane (see column 16, lines 50-65 in particular). US Patent '368 does not teach specific types of engineered cytokine or specific opsonin-enhanced cells as recited in claims 3-8 and 20.

The Known fact disclosed in the Specification on pages 52-54 and 66 – 68 teaches that it is conventional and within the skill of the art to produce : (i) an opsonin-enhanced cells, wherein opsonin of said cells is mannose binding protein or alph' chain of C3b to allow more efficient binding, engulfment and internalization of the antigen; (ii) an engineered cytokine by attaching the lipid , e.g. a lond-chain fatty acid, for example palmitate or GPI moiety to said cytokine to permit a complex to become stable associated with plasma membrane.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of the Known fact disclosed in the Specification on pages 52-54 and 66 – 68 to those of US Patent '368 to obtain a claimed method of vaccinating a mammal to a selected antigen, comprising administering vaccine composition comprising an opsonin-enhanced cells and engineered cytokine comprising a lipid or GPI moiety or palmitate.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because engineered cytokine wherein lipid , e.g. a lond-chain fatty acid, for example palmitate or GPI moiety is attached to said cytokine permits said complex to become stable associated with plasma membrane of the cell and an opsonin-enhanced of said cells, allows more efficient binding, engulfment and internalization of said engineered cytokine into said cell as taught by the known fact disclosed in the Specification on pages 52-54 and 66-68. Thus the "cytokine-coated cells " will be obtained that can be further used by the method taught by US patent '368.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
April 21, 2003

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